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MOLECULAR EPIDEMIOLOGY OF THE COMMUNITY-ASSOCIATED METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS CLONES: A SYNTHETIC REVIEW

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Abstract

The article presents a synthetic molecular characterization of the methicillin-resistant Staphylococcus aureus and describes the most important community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) clones that circulate nowadays in the world: the main molecular and epidemiological characteristics, as well as notions related to the clinic of infections produced by these clones and their antibiotic resistance spectrum.

The predominant clone of CA-MRSA in North America is USA300 – ST8-IV in North America, in Australia – Queensland (Qld) MRSA (ST93-IV), in Europe – ST80-IV, in Asia there is a high heterogeneity of clones population, in Africa the distribution of CA-MRSA clones is unclear, and in South America – USA 1100 and USA300-Latin American variant are predominant.

The molecular diagnosis is performed by highly specialized institutions. The knowledge of clones allows the study of antibiotic resistance spectrum for each one, a fact of great importance for medical practice. Molecular epidemiology of the CA-MRSA shows that lowly restricted sales of antibiotics in shops and pharmacies, as well as medical prescribing practices without a laboratory investigation, especially in Eastern Europe and Asia, contribute to the development of new MRSA clones with increased resistance to antibiotics.

Keywords: *Staphylococcus aureus*, CA-MRSA, clones

Introduction

Staphylococcus aureus is a gram-positive bacterium, the most commonly isolated bacterial human pathogen [1]. Although *Staphylococcus aureus* is considered an opportunistic pathogen, there are clones which can cause invasive disease, due to the presence of virulence factors that increase their chance of gaining access to normally sterile sites [2].

In 1961, soon after the introduction of methicillin, strains of *Staphylococcus aureus* that were resistant were identified in the United Kingdom [3] and were called Methicillin-resistant *Staphylococcus aureus* - MRSA. Until the year 1990, MRSA became endemic in university hospitals in the United States, particularly in Intensive Care Units [4]. Since the 1990s, there has been an explosion of MRSA infections in populations with no risk of exposure to the health care system - later called community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) [5], first reported in Australia and the United States [6].

There have been multiple attempts at differentiating of CA-MRSA from health care-associated MRSA (HA-MRSA). Clinically, CA-MRSA infection is defined as any MRSA infection diagnosed in an outpatient or within 48 h of hospitalization if the patient lacks the following HA-MRSA risk factors: haemodialysis, surgery, residence in a long-term-care facility. or hospitalization during the previous year, the presence of an indwelling catheter or

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percutaneous device at the time of culture, or previous isolation of MRSA from the patient [7,8]. However, clinical distinction between CA-MRSA and HA-MRSA remains difficult [9].

CA-MRSA strains differ from HA-MRSA strains in their molecular characteristics.

HA-MRSA strains have a relatively large mobile genomic island, Staphylococcal Chromosomal Cassette (SCCmec), belonging to type I, II, or III. These cassettes contain the mecA gene, which is nearly universal among MRSA isolates and is responsible for resistance to antibiotics. HA-MRSA are resistant to many classes of non-β-lactam antimicrobials. HA-MRSA has seldom the genes Panton-Valentine leukocidin (PVL) [4,10].

CA-MRSA carry smaller SCCmec elements, type IV or type V. These smaller elements carry the mecA gene and are more mobile. They are resistant to fewer non-β-lactam classes of antimicrobials and frequently carry PVL genes [4]. CA-MRSA clones are known to be more virulent than HA-MRSA [11].

CA-MRSA affect previously healthy younger patients and can cause necrotizing pneumonia and severe sepsis. HA-MRSA affect people who are exposed to the health care setting, older patients with comorbidities, through pneumonia, bacteremia, and invasive infections [4].

Given the complex epidemiology of CA-MRSA strains in hospital and the circulation of HA-MRSA strains in the community, a clear delineation between CA-MRSA and HA-MRSA strains is not possible [4].

We describe the most important CA-MRSA clones that circulate nowadays in the world: the main molecular and epidemiological characteristics, as well as notions related to the clinic of infections produced by these clones and their antibiotic resistance spectrum.

The main clones of CA-MRSA in the world

Multilocus sequence typing reveals a highly clonal structure for Staphylococcus aureus. Comparison of commensal and pathogenic strains shows no difference in diversity or clonal assignments, phage dynamics and global transcriptome shifts are considered responsible for the pathogenicity [12].

Beginning in 1993, the MRSA infections of patients lacking health care-associated risk factors were reported from six continents, in diverse regions. Molecular evidence supports that CA-MRSA clones have arisen in the community by the horizontal transfer of SCCmec elements and PVL genes, as well as perhaps other virulence and resistance factors, to the genomes of MRSA strains. Thus, CA-MRSA strains developed in several decades of complex evolution [2].

Experimental studies show recombination to have negligible impact on the diversification of the core genome of this species. the vast majority of clonal variants arise by point mutation. Recombination combined with demographic mechanisms and selection favor the rapid creation of new clonal complexes [13].

North America. CA-MRSA epidemic in the United States is attributable to rise of a clone, referred to as USA300 – ST8-IV (Figure 1), a virulent and easily transmissible strain of MRSA. It most commonly causes skin infections, but also necrotizing pneumonia or endocarditis [14,15].

A recent study shows that United States households represent a frequent site of transmission and a long-term reservoir of USA300 strains; individuals within households transmit the same USA300 strain among themselves. A large proportion of the USA300 isolates in this study sequenced are resistant to fluoroquinolone [15].

Military are at increased risk for MRSA skin and soft tissue infection. A study shows there is a transmission of MRSA among military trainees and suggests a long-term reservoir for MRSA in this setting [16].

USA300 emerge first in community and then in healthcare settings. Most USA300 retain typical susceptibility profiles, but multidrug-resistant phenotypes are emerging. This clone is disseminated on every continent, except Antarctica [4].

The epidemiology of MRSA in North America is much better studied and described than the European one.

Australia. The percentage of MRSA has increased from 10.3% in 2000 to 16% in 2006. This increase has occurred throughout Australia and has been due to CA-MRSA clones. The predominate clone is Queensland (Qld) MRSA (ST93-IV) – figure 1, a Panton-Valentine leukocidin (PVL) positive MRSA, the same as USA300. With transmission of Qld MRSA throughout the country, an increase in skin and soft tissue infections will occur in young Australians [17]. In Western Australia, ST835 CA-MRSA is isolated almost exclusively from elderly care facilities [18].

Europe. The prevalence of CA-MRSA in Europe seems to be less, especially in the Nordic countries [19]. In Greece, rates of CA-MRSA in some centers approach those of North America. In contrast to North America, CA-MRSA in Europe is characterized by bigger clonal heterogeneity. The predominant European clone is ST80-IV (Figure 1), resistant to kanamycin/amikacin and fusidic acid [20-21], strongly associated with skin and soft tissue infections, rarely found among asymptomatic carriers. ST80 was first reported in 1993, but was relatively rare until the late 1990s [22].

Phylogenetic analyses strongly suggest that the European epidemic CA-MRSA lineage is derived from a PVL-positive MRSA ancestor from sub-Saharan Africa. The tree topology suggests a single acquisition of both the SCCmec element and a plasmid encoding the fusidic acid resistance. These changes were associated with human migrations [22].

ST80 has been identified throughout North Africa, the Middle East, and Europe, with sporadic reports in sub-

Saharan Africa [22].

For European children, PVL is associated with more severe infections, regardless of methicillin resistance [23].

An European multicentric study shows the USA300 clone is not common among community-infected patients in Europe [24].

Asia. Asia is among the regions with the highest incidence of MRSA in the world. Most reports on the epidemiology of CA-MRSA are from developed countries; the molecular epidemiology of CA-MRSA in Asia is characterized by clonal heterogeneity (Figure 1), similar to that in Europe [25], but a dominant clone has not been identified. In certain countries, Vancomycin-intermediate *Staphylococcus aureus* strains and vancomycin-resistant *Staphylococcus aureus* strains are being increasingly identified [26,27]. In India, CA-MRSA clones manifest through severe soft tissue and skin infections requiring surgical drainage, bacteremias affecting neonates, especially from lower economic sections, and breast abscesses in lactating mothers [28].

Africa. The distribution of CA-MRSA clones in general is unclear [29] and the dates are insufficient. The first information about characterization of MRSA in Egypt were published PubMed in 2015 [30].

ST88-IV African CA-MRSA clone, from Ghana, forms a discrete MRSA lineage, with resistence to β-lactams, tetracycline and chloramphenicol [6].

South America. In South America, two predominant CA-MRSA clones have been reported: ST30-SCCmecIV or USA 1100 (first found in Uruguay in 2002 and later in Brazil and Argentina in 2005), and ST8-IV or USA300-Latin American variant (found predominantly in Ecuador and Colombia in 2006–2008) – figure 1 [31,32].

The European ST80 clone is limited to Algeria, Egypt and Tunisia [29]. In Colombia, several genetic and molecular analyses have shown that the most prevalent CA-MRSA clone is USA300-Latin American [33]. In Rio de Janeiro, USA300, USA400, USA600, USA800 and USA1100 were identified [34]. CA-MRSA seems to have a low incidence in Brazil [35] and Peru [36].

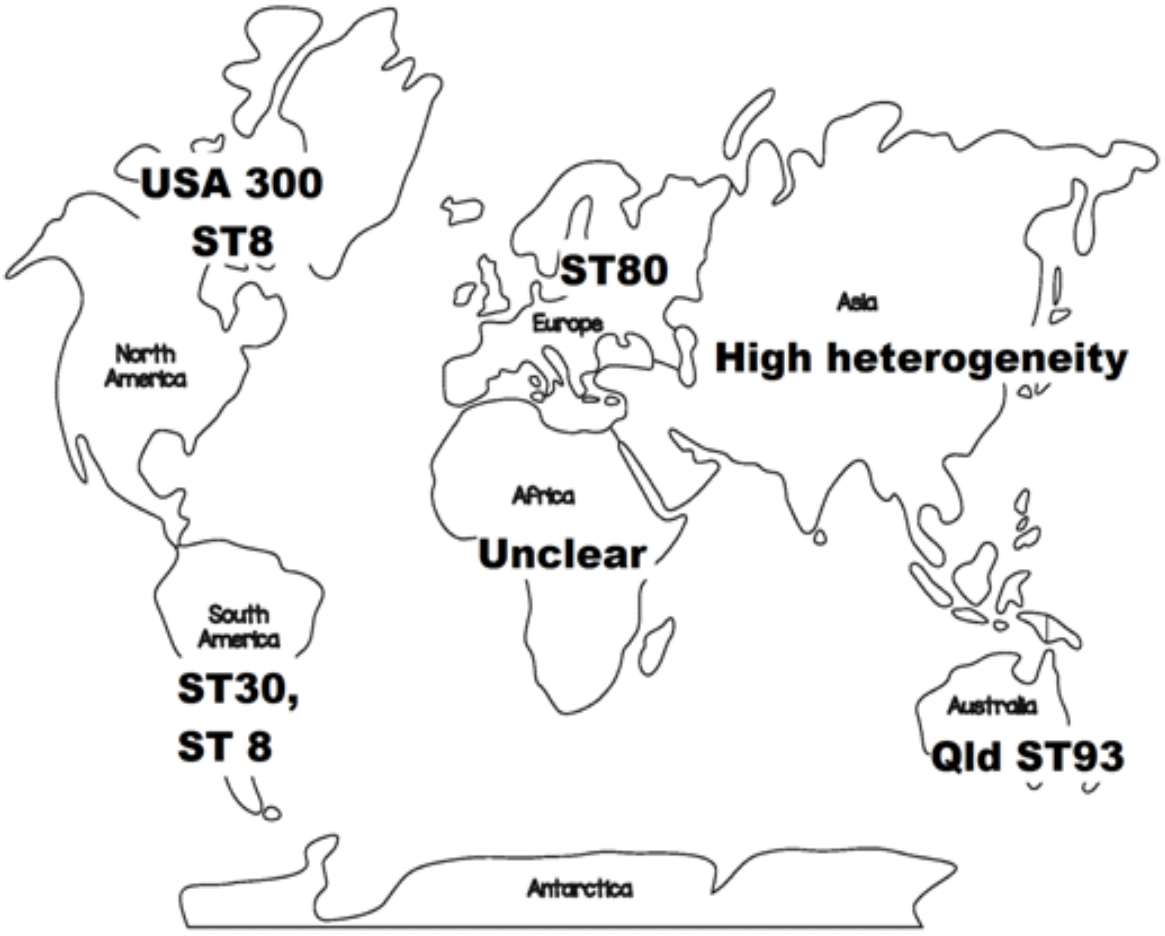

Figure 1. Schematic map of the main CA-MRSA clones.

Conclusions

MRSA epidemiology is changing rapidly due to the continuous development of clones. In turn, it is influenced through the deficient therapeutic management of infectious diseases, through auto-medication, especially in Eastern Europe and Asia. The lowly restricted sales of antibiotics in shops and pharmacies, as well as medical prescribing practices without a laboratory investigation contribute to the development of new MRSA clones with increase resistance to antibiotics.

The epidemiology of MRSA in North America is much better studied and described than the European one. USA300 – ST8-IV, the predominant North American clone, has become quite well controlled with antibiotics today, but multidrug-resistant phenotypes are emerging. In South America, USA 1100 and USA300-Latin American variants are predominant clones.

In contrast to North America, CA-MRSA in Europe is characterized by bigger clonal heterogeneity. The predominant European clone, ST80-IV, is resistant to kanamycin/amikacin and fusidic acid, and is strongly associated with skin and soft tissue infections. Asia is characterized by clonal heterogeneity, similar to that in Europe, but a dominant clone has not been identified. In India, CA-MRSA clones manifests especially from lower economic sections. For Africa, the dates are insufficient.

The knowledge of clones allows studying antibiotics resistance spectrum for each one, a fact of great importance for medical practice.

Appropriate prevention, risk factors and natural history of staphylococcal infections are not fully elucidated. Therefore, it is necessary to monitor antibiotic resistance, judicious organization of antibiotics prescription and therapy of infectious-contagious disease, medical education of travelers and immigrants.

The molecular diagnosis is performed by highly specialized institutions, but basic laboratory diagnosis is accessible to any hospital and should not be neglected. Genotypic isolate characteristics are not helpful for a clinician caring for an acutely ill patient, but basic microbiological diagnosis can save the patient from death.

References

1. Lowy FD. Staphylococcus aureus infections. N Engl J Med. 1998;339(8):520-532.
2. Feil EJ, Cooper JE, Grundmann H, Robinson DA, Enright MC, Berendt T, et al. How clonal is Staphylococcus aureus? J Bacteriol. 2003;185(11):3307-3316.
3. Jevons MP. "Celbenin"-resistant staphylococci. BMJ. 1961;1:124-125.
4. David MZ, Daum RS. Community-associated methicillin-resistant Staphylococcus aureus: epidemiology and clinical consequences of an emerging epidemic. Clin Microbiol Rev. 2010;23(3):616-687.
5. Ellis MW, Hospenthal DR, Dooley DP, Gray PJ, Murray CK. Natural history of community-acquired methicillin-resistant Staphylococcus aureus colonization and infection in soldiers. Clin Infect Dis. 2004;39(7):971-979.
6. Kpeli G, Buultjens AH, Giulieri S, Owusu-Mireku E, Aboagye SY, Baines SL, et al. Genomic analysis of ST88 community-acquired methicillin resistant Staphylococcus aureus in Ghana. PeerJ. 2017 Feb 28;5:e3047. doi: 10.7717/peerj.3047.
7. Morrison MA, Hageman JC, Klevens RM. Case definition for community-associated methicillin-resistant Staphylococcus aureus. J Hosp Infect. 2006 Feb;62(2):241.
8. Centers for Disease Control and Prevention. Community associated MRSA information for clinicians. Infection control topics. Atlanta, 2005.
9. Chen CJ, Huang YC. New epidemiology of Staphylococcus aureus infection in Asia. Clin Microbiol Infect. 2014;20(7):605-623.
10. Deurenberg RH, Stobberingh EE. The molecular evolution of hospital- and community-associated methicillin-resistant Staphylococcus aureus. Curr Mol Med. 2009;9(2):100-115.
11. Chua KY, Monk IR, Lin YH, Seemann T, Tuck KL, Porter JL, et al. Hyperexpression of α-hemolysin explains enhanced virulence of sequence type 93 community-associated methicillin-resistant Staphylococcus aureus. BMC Microbiol. 2014 Feb 10;14(1):31. doi: 10.1186/1471-2180-14-31.
12. Feng Y, Chen CJ, Su LH, Hu S, Yu J, Chiu CH. Evolution and pathogenesis of Staphylococcus aureus: lessons learned from genotyping and comparative genomics. FEMS Microbiol Rev. 2008;32(1):23-37.
13. Basic-Hammer N, Vogel V, Basset P, Blanc DS. Impact of recombination on genetic variability within Staphylococcus aureus clonal complexes. Infect Genet Evol. 2010;10(7):1117-1123.
14. Planet PJ. Life After USA300: The Rise and Fall of a Superbug. J Infect Dis. 2017;215(suppl_1):S71-S77.
15. Alam MT, Read TD, Petit RA 3rd, Boyle-Vavra S, Miller LG, Eells SJ, et al. Transmission and microevolution of USA300 MRSA in U.S. households: evidence from whole-genome sequencing. MBio. 2015 Mar 10;6(2):e00054. doi: 10.1128/mBio.00054-15.
16. Millar EV, Rice GK, Elassal EM, Schlett CD, Bennett JW, Redden CL, et al. Genomic Characterization of USA300 Methicillin-Resistant Staphylococcus aureus (MRSA) to Evaluate Intraclass Transmission and Recurrence of Skin and Soft Tissue Infection (SSTI) among High-Risk Military Trainees. Clin Infect Dis. 2017;65(3):461-468.
17. Coombs GW, Nimmo GR, Pearson JC, Christiansen KJ, Bell JM, Collignon PJ, et al. Prevalence of MRSA strains among Staphylococcus aureus isolated from outpatients, 2006. Commun Dis Intell Q Rep. 2009;33(1):10–20.
18. Wilson LK, Coombs GW, Christiansen K, Grubb WB, O'Brien FG. Characterization of a novel staphylococcal cassette chromosome composite island from community-associated MRSA isolated in aged care facilities in Western Australia. J Antimicrob Chemother. 2016;71(12):3372-3375.
19. Dahlman D, Berge J, Nilsson AC, Kral AH, Bjorkman P, Hakansson AC. Opioid and amphetamine dependence is associated with methicillin-resistant Staphylococcus aureus (MRSA): An epidemiological register study with 73,201 Swedish in- and outpatients 1997-2013. Infect Dis (Lond). 2017;49(2):120-127.
20. Otter JA, French GL. Molecular epidemiology of community-associated meticillin-resistant Staphylococcus aureus in Europe. Lancet Infect Dis. 2010;10(4):227–239.

21. Doudoulakakis AG, Bouras D, Drougka E, Kazantzi M, Michos A, Charisiadou A, et al. Community-associated Staphylococcus aureus pneumonia among Greek children: epidemiology, molecular characteristics, treatment, and outcome. Eur J Clin Microbiol Infect Dis. 2016;35(7):1177-1185.
22. Stegger M, Wirth T, Andersen PS, Skov RL, De Grassi A, Simões PM, et al. Origin and evolution of European community-acquired methicillin-resistant Staphylococcus aureus. MBio. 2014;5(5):e01044-14. doi: 10.1128/mBio.01044-14.
23. Gijón M, Bellusci M, Petraitiene B, Noguera-Julian A, Zilinskaite V, Sanchez Moreno P, et al. Factors associated with severity in invasive community-acquired Staphylococcus aureus infections in children: a prospective European multicentre study. Clin Microbiol Infect. 2016;22(7):643.e1-e6. doi: 10.1016/j.cmi.2016.04.004.
24. Bouchiat C, Curtis S, Spiliopoulou I, Bes M, Cocuzza C, Codita I, et al. MRSA infections among patients in the emergency department: a European multicentre study. J Antimicrob Chemother. 2017;72(2):372-375.
25. Chuang YY, Huang YC. Molecular epidemiology of community-associated meticillin-resistant Staphylococcus aureus in Asia. Lancet Infect Dis. 2013;13:698–708.
26. Saha B, Singh AK, Ghosh, A, Bal M. Identification and characterization of a vancomycin-resistant Staphylococcus aureus isolated from Kolkata (South Asia). J Med Microbiol. 2008;57(Pt 1):72–79.
27. Tiwari HK, Sen MR. Emergence of vancomycin resistant Staphylococcus aureus (VRSA) from a tertiary care hospital from northern part of India. BMC Infect Dis. 2006;6:156.
28. D'Souza N, Rodrigues C, Mehta A. Molecular characterization of methicillin-resistant Staphylococcus aureus with emergence of epidemic clones of sequence type (ST) 22 and ST 772 in Mumbai, India. J Clin Microbiol. 2010;48(5):1806-1811.
29. Abdulgader SM, Shittu AO, Nicol MP, Kaba M. Molecular epidemiology of methicillin-resistant Staphylococcus aureus in Africa: a systematic review. Front Microbiol. 2015 Apr 30;6:348. doi: 10.3389/fmicb.2015.00348.
30. Abd El-Hamid MI, Bendary MM. Comparative phenotypic and genotypic discrimination of methicillin resistant and susceptible Staphylococcus aureus in Egypt. Cell Mol Biol (Noisy-le-grand). 2015;61(4):101-112.
31. García C, Astocondor L, Reyes J, Carvajal LP, Arias CA, Seas C. Community-Associated MRSA Infection in Remote Amazon Basin Area, Peru. Emerg Infect Dis. 2016;22(5):921-922.
32. Reyes J, Rincón S, Díaz L, Panesso D, Contreras GA, Zurita J, et al. Dissemination of methicillin-resistant Staphylococcus aureus USA300 sequence type 8 lineage in Latin America. Clin Infect Dis. 2009;49(12):1861-1867.
33. Escobar-Perez J, Reyes N, Marquez-Ortiz RA, Rebollo J, Pinzón H, Tovar C, et al. Emergence and spread of a new community-genotype methicillin-resistant Staphylococcus aureus clone in Colombia. BMC Infect Dis. 2017 Jan 31;17(1):108. doi: 10.1186/s12879-017-2193-3.
34. Zuma AV, Lima DF, Assef AP, Marques EA, Leão RS. Molecular characterization of methicillin-resistant Staphylococcus aureus isolated from blood in Rio de Janeiro displaying susceptibility profiles to non-β-lactam antibiotics. Braz J Microbiol. 2017;48(2):237-241.
35. Bodnar GC, Martins HM, De Oliveira CF, Morey AT, Tavares ER, Cardoso JD, et al. Comparison of HRM analysis and three REP-PCR genomic fingerprint methods for rapid typing of MRSA at a Brazilian hospital. J Infect Dev Ctries. 2016;10(12):1306-1317.
36. García C, Deplano A, Denis O, León M, Siu H, Chincha O, et al. Spread of community-associated methicillin-resistant Staphylococcus aureus to Peru. J Infect. 2011;63(6):482-483.